

[0006] One particular concern that has arisen in the context of treatments for AD, is the occurrence of imaging abnormalities believed to represent cerebral vasogenic edema and microhemorrhage. These abnormalities have been reported in association with the investigational use of immunotherapy targeting the amyloid beta peptide, possibly by interacting with amyloid beta deposited in or around blood vessels and eliciting an immune response. These abnormalities have been observed to be dose-dependent, arising with more frequency the higher the dose of antibody administered. *See, e.g.,* Sevigny et al., 2016, *Nature*. 537:50-6. Symptoms, when present in association with such imaging abnormalities, have been reported to include headache, worsening cognitive function, alteration of consciousness, seizures, unsteadiness, and vomiting (Salloway et al. 2009, *Neurology* 73:2061–70; Sperling et al. 2011, *Alzheimers Dement* 7:367–85). Tau pathology occurs primarily intracellularly in the cytoplasm of diseased neurons (Braak et al. 2006), and soluble extracellular Tau is found in the cerebrospinal fluid (Blennow and Zetterberg 2009). Unlike A β , Tau is not known to deposit in vascular structures, however, it is not known whether targeting Tau in the human brain could elicit the types of dose-dependent side effects observed with some anti-amyloid beta immunotherapy, especially when administering high doses of Tau immunotherapy.

SUMMARY

[0007] The disclosure provides methods of treating neurodegenerative diseases with anti-Tau antibodies. As described herein, Applicants have discovered that immunotherapy with antibodies that bind Tau is safe and tolerated even when administered at high doses to both healthy volunteers and patients suffering from AD.

[0008] In some examples, a method of treating a neurodegenerative disease comprises administering an isolated antibody that binds to human Tau, wherein the antibody binds to monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau. In some examples, the antibody binds an epitope within amino acids 2 to 24 of mature human Tau. In some examples, the antibody is a monoclonal antibody. In some examples, the antibody is a human, humanized, or chimeric antibody. In some examples, the antibody is an antibody fragment that binds human Tau. In some examples, the human Tau comprises the sequence of SEQ ID NO: 2.

[0009] In some examples, the antibody comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 20; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 21; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 22; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 23; HVR-L2 comprising the amino acid

sequence of SEQ ID NO: 24; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 25.

[0010] In some examples, the antibody comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 20; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 21; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 22; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 23; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 24; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 25.

[0011] In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 18 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 19.

[0012] In some examples, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 26 or SEQ ID NO: 27 and a light chain comprising the amino acid sequence of SEQ ID NO: 28. In some examples, the hMTAU antibody described herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 27 and a light chain comprising the amino acid sequence of SEQ ID NO: 28.

[0013] In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 26 or SEQ ID NO: 27 and a light chain comprising the amino acid sequence of SEQ ID NO: 28. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 26 and a light chain comprising the amino acid sequence of SEQ ID NO: 28. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 27 and a light chain comprising the amino acid sequence of SEQ ID NO: 28. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 26 or SEQ ID NO: 27 and a light chain consisting of the amino acid sequence of SEQ ID NO: 28. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 26 and a light chain consisting of the amino acid sequence of SEQ ID NO: 28. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 27 and a light chain consisting of the amino acid sequence of SEQ ID NO: 28. The isolated antibodies described herein may be used in methods of treating a Tau protein associated disease. The isolated antibodies described

herein may be used in methods of slowing memory loss or retaining or increasing memory capacity, memory function, or cognitive function in an individual. The isolated antibodies described herein may be used in methods of reducing the level of Tau protein.

[0014] In any of the examples described herein, the antibody may be an IgG1 or an IgG4 antibody. In any of the examples described herein, the antibody may be an IgG4 antibody. In some such examples, the antibody comprises M252Y, S254T, and T256E mutations. In any of the examples described herein, the antibody may comprise an S228P mutation. In any of the examples described herein, the antibody may comprise S228P, M252Y, S254T, and T256E mutations. In any of the examples described herein, the antibody may be an IgG4 antibody comprising S228P, M252Y, S254T, and T256E mutations. In some examples, the antibody is an antibody fragment. In any of the examples described herein, the antibody may be an IgG4 antibody comprising S228P, M252Y, S254T, and T256E mutations, and lacking the C-terminal lysine of the heavy chain constant region. The C-terminal lysine of the heavy chain constant region may be removed, for example, during purification of the antibody or by recombinant engineering of the nucleic acid encoding the antibody such that the C-terminal lysine is not encoded.

[0015] In some examples, an isolated antibody that binds human Tau is provided, wherein the antibody binds each of monomeric Tau, phosphorylated Tau, non-phosphorylated Tau, and oligomeric Tau with a K_D of less than 100 nM, less than 75 nM, or less than 50 nM. In some examples, the antibody binds cynomolgus monkey Tau (SEQ ID NO: 4).

[0015a] In one aspect, the present disclosure refers to use of a monoclonal antibody that binds human tau at a dose between 225 mg and 16800 mg, in the manufacture of a medicament for treating a Tau protein associated disease in an individual with a Tau protein associated disease, wherein the antibody comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 20; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 21; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 22; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 23; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 24; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 25.

[0016] In some examples, a method of treating a Tau protein associated disease is provided, comprising administering to an individual with a Tau protein associated disease an antibody described herein or a pharmaceutical composition comprising an antibody described herein. In some examples, the Tau protein associated disease is a tauopathy. In some examples, the tauopathy is a neurodegenerative tauopathy. In some examples, the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia,

Postencephalitic Parkinsonism, and Myotonic dystrophy. In some examples, the tauopathy is Alzheimer's Disease (AD) or progressive supranuclear palsy. In some examples, the AD is early, prodromal, prodromal to mild, mild, mild to moderate or moderate.

[0017] In some examples, treating a Tau protein associated disease comprises slowing memory loss or retaining or increasing memory capacity, memory function, or cognitive function in the individual.

[0018] In some examples, a method of slowing memory loss or retaining or increasing memory capacity, memory function, or cognitive function in an individual is provided, comprising administering an antibody described herein or a pharmaceutical composition comprising an antibody described herein.

[0019] In some examples, memory capacity, memory function, cognitive function, or memory loss is assessed using one or more of Clinical Dementia Rating–Sum of Boxes (CDR-SB), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog). In some examples, ADAS-Cog is ADAS-Cog 13.

[0020] In some examples, a decrease in CDR-SB score, or an increase in RBANS score, or a decrease in ADAS-Cog score following administration of one or more doses of the antibody indicates increased cognitive memory capacity in the individual. In some examples, a stable CDR-SB score, RBANS score, or ADAS-Cog score following administration of one or more doses of the antibody indicates retained memory capacity, memory function, cognitive function, or slowed memory loss in the individual. In some examples, a slowing of the rate of increase of a CDR-SB score or ADAS-Cog score, or a slowing of the rate of decrease of a RBANS score indicates retained memory capacity, memory function, cognitive function, or slowed memory loss in the individual.

[0021] In some examples, the CDR-SB score, RBANS score, or ADS-Cog score is compared to the respective score at baseline. In some examples, baseline is prior to administration of the antibody. In some examples, the memory capacity, memory function, cognitive function, or memory loss is assessed at least 13 weeks, at least 24 weeks, at least 25 weeks, at least 37 weeks, at least 49 weeks, at least 61 weeks, at least 69 weeks, at least 73 weeks, at least 85 weeks, at least 97 weeks, at least 109 weeks, at least 121 weeks, at least 133 weeks, at least 145 weeks, at least 157 weeks, or at least 169 weeks after the beginning of treatment with the antibody.

[0021a] In one aspect, the present disclosure refers to use of a monoclonal antibody that binds human tau at a dose between 225 mg and 16800 mg, in the manufacture of a medicament for reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual with a Tau protein associated disease, wherein the antibody comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 20; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 21; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 22; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 23; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 24; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 25.

[0022] In some examples, a method of reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein

in an individual is provided, comprising administering an antibody described herein or a pharmaceutical composition comprising an antibody described herein.

[0023] In some examples, an isolated antibody described herein is provided for use as a medicament. In some examples, an isolated antibody described herein is provided for use in treating a tauopathy in an individual. In some examples, the tauopathy is a neurodegenerative tauopathy. In some examples, the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy. In some examples, the tauopathy is Alzheimer's Disease (AD) or progressive supranuclear palsy. In some examples, the AD is AD is early, prodromal, prodromal to mild, mild, mild to moderate or moderate.

[0023a] In one aspect, the present disclosure refers to use of a monoclonal antibody that binds human tau at a dose between 225 mg and 16800 mg, in the manufacture of a medicament for retaining or increasing one or more of memory capacity, memory function, or cognitive function or slowing memory loss in an individual with a Tau protein associated disease, wherein the antibody comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 20; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 21; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 22; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 23; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 24; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 25.

[0024] In some examples, an isolated antibody described herein is provided for use in slowing memory loss or retaining or increasing memory capacity, memory function, or cognitive function in an individual. In some examples, an isolated antibody described herein is provided for use in reducing the level of Tau protein, phosphorylated Tau protein, non-phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual.

[0025] In some examples, use of an antibody described herein is provided for manufacture of a medicament for treating a Tau protein associated disease in an individual. In some examples, the Tau protein associated disease is a tauopathy. In some examples, the tauopathy is a neurodegenerative tauopathy. In some examples, the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome

17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy. In some examples, the tauopathy is Alzheimer's disease or progressive supranuclear palsy. In some examples, the AD is AD is early, prodromal, prodromal to mild, mild, mild to moderate or moderate.

[0026] In some examples, use of an antibody described herein is provided for manufacture of a medicament for slowing memory loss or retaining or increasing memory capacity, memory function, or cognitive function in an individual.

[0027] In some examples, a method of detecting neurofibrillary tangles, neutrophil threads, or dystrophic neuritis is provided, comprising contacting a sample with an antibody described herein. In some examples, the sample is a brain sample, a cerebrospinal fluid sample, or a blood sample.

[0028] In any of the examples described herein, a method or use may comprise administering an antibody described herein in combination with at least one additional therapy. Non-limiting examples of additional therapies include neurological drugs, corticosteroids, antibiotics, antiviral agents, and other therapeutic agents. Such other therapeutic agents include, but are not limited to, other anti-Tau antibodies, antibodies against amyloid-beta, antibodies against a beta-secretase ("BACE") such as antibodies against beta-secretase 1 ("BACE1") or antibodies against beta-secretase 2 ("BACE2"), and inhibitors of a beta-secretase, such as inhibitors of beta-secretase 1 or inhibitors of beta-secretase 2.

[0029] In some examples, the antibody is administered at a dose of 225 mg, 675 mg, 1200 mg, 1500 mg, 2100 mg, 4200 mg, 4500 mg, 8100 mg, 8400 mg, or 16800 mg. In some examples, the antibody is administered at a dose between 225 mg and 1000 mg. In some examples, the antibody is administered at a dose between 225 mg and 600 mg. In some examples, the antibody is administered at a dose between 600 mg and 1000 mg. In some examples, the antibody is administered at a dose between 1000 mg and 2000 mg. In some examples, the antibody is administered at a dose between 2000 mg and 3000 mg. In some examples, the antibody is administered at a dose between 3000 mg and 4000 mg. In some examples, the antibody is administered at a dose between 4000 mg and 16800 mg. In some instances, the antibody may be administered at a dose between 4000 mg and 8500 mg. In some examples, the antibody is administered at a dose between 4000 mg and 4500 mg, 4000 mg and 5000 mg, 4500 mg and 5000 mg, 5000 mg and 5500 mg, 5500 mg and 6000 mg, 6000 mg and 6500 mg, 6500 mg and 7000 mg, 7000 mg and 7500 mg, 7500 mg and 8000 mg, or 8000 mg and 8500 mg.

[0030] In some examples, the antibody is administered at a dose between 2.5 mg/kg and 5 mg/kg, 5 mg/kg and 10 mg/kg, 10 mg/kg and 15 mg/kg, 15 mg/kg and 20 mg/kg, 20 mg/kg and 30 mg/kg, 30 mg/kg and 40 mg/kg, 40 mg/kg and 50 mg/kg, 50 mg/kg and 60 mg/kg, 50 mg/kg and 240 mg/kg. In some instances, the antibody is administered at a dose between 60 mg/kg and 120 mg/kg. In some examples, the antibody is administered at a dose between 60 mg/kg and 70 mg/kg, 70 mg/kg and 80 mg/kg, 80 mg/kg and 90 mg/kg, 90 mg/kg and 100 mg/kg, 100 mg/kg and 110 mg/kg, or 110 mg/kg and 120 mg/kg.

[0031] In some examples, the methods and uses described herein comprise administering the antibody once every 2, 4, 5, 6, 7, or 8 weeks. In some instances, the antibody is administered twice every 2, 4, 5, 6, 7, or 8 weeks.

[0032] In some examples, the methods and uses described herein comprise administering the antibody subcutaneously. In some instances, the methods and uses comprise administering the antibody intravenously.

[0032a] In one aspect, the present disclosure refers to anti-Tau antibody comprising HVR-H1 comprising the amino acid sequence of SEQ ID NO: 20; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 21; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 22; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 23; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 24; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 25 provided at a dose between 225 mg and 16800 mg for use in 1) treating a Tau protein associated disease; 2) reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein; or 3) slowing memory loss or retaining or increasing memory capacity, memory function, or cognitive function in an individual.

[0032b] In one aspect, the present disclosure refers to use of an anti-Tau antibody comprising HVR-H1 comprising the amino acid sequence of SEQ ID NO: 20; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 21; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 22; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 23; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 24; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 25 for the manufacture of a medicament for 1) treating a Tau protein associated disease; 2) reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein; or 3) slowing memory loss or retaining or increasing memory capacity, memory function, or cognitive function in an individual, wherein the antibody is provided at a dose between 225 mg and 16800 mg.

BRIEF DESCRIPTION OF THE FIGURES

[0033] FIG 1 shows the overall study design, including the single dose escalation stage and the multiple dose stage of the clinical study in Example 1. Abbreviations used in the figure as follows: DLAE, dose-limiting adverse event; HV, healthy volunteers; AD, Alzheimer's Disease; IV, intravenous; SC, subcutaneous; CSF, cerebrospinal fluid.

[0034] FIG 2 provides mean ($\pm$ SD) concentration-time profiles of hMTAU in serum after single dose IV or SC administration.

[0035] FIG 3 provides mean ($\pm$ SD) concentration-time profiles of hMTAU in CSF after single dose 2100 and 8400 mg IV administration.

[0036] FIG 4 provides mean ($\pm$ SD) concentration-time profiles of hMTAU in serum after single or multiple dose IV or SC administration.

[0037] FIG 5 provides mean ($\pm$ SD) concentration-time profiles of hMTAU in CSF after single dose 2100 and 8400 mg IV administration and multiple dose 8400 mg IV administration.

[0038] FIG 6 provides mean ($\pm$ SD) concentration-time profiles of hMTAU in serum (left axis) and mean ($\pm$ SD) concentration-time profiles of TAU in plasma (right axis) after four weekly doses of hMTAU at 8400 mg IV. PK (pharmacokinetics) and PD (pharmacodynamics) concentration-time profiles are shown. AD = patients with Alzheimer's disease; HV = healthy volunteers.

[0039] FIG 7 shows a design for a clinical study of hMTAU in prodromal-to-mild Alzheimer's disease patients.

WHAT IS CLAIMED IS:

1. Use of a monoclonal antibody that binds human tau at a dose between 225 mg and 16800 mg, in the manufacture of a medicament for treating a Tau protein associated disease in an individual with a Tau protein associated disease, wherein the antibody comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 20; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 21; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 22; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 23; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 24; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 25.
2. The use of claim 1, wherein the antibody is to be administered at a dose of 225 mg, 675 mg, 1200 mg, 1500 mg, 2100 mg, 4200 mg, 4500 mg, 8100 mg, 8400 mg, or 16800 mg.
3. The use of claim 1, wherein the antibody is to be administered at a dose between 4000 mg and 16800 mg.
4. The use of claim 1, wherein the antibody is to be administered at a dose between 4000 mg and 8500 mg.
5. The use of claim 1, wherein the antibody is to be administered at a dose between 225 mg and 600 mg, 600 mg and 1000 mg, 1000 mg and 2000 mg, 2000 mg and 3000 mg, 3000 mg and 4000 mg, 4000 mg and 4500 mg, 4000 mg and 5000 mg, 4500 mg and 5000 mg, 5000 mg and 5500 mg, 5500 mg and 6000 mg, 6000 mg and 6500 mg, 6500 mg and 7000 mg, 7000 mg and 7500 mg, 7500 mg and 8000 mg, or 8000 mg and 8500 mg.
6. The use of claim 1, wherein the antibody is to be administered at a dose between 50 mg/kg and 240 mg/kg.
7. The use of claim 1, wherein the antibody is to be administered at a dose between 60 mg/kg and 120 mg/kg.
8. The use of claim 1, wherein the antibody is to be administered at a dose between 2.5 mg/kg and 5 mg/kg, 5 mg/kg and 10 mg/kg, 10 mg/kg and 15 mg/kg, 15 mg/kg and 20 mg/kg, 20 mg/kg and 30 mg/kg, 30 mg/kg and 40 mg/kg, 40 mg/kg and 50 mg/kg, 50 mg/kg and 60 mg/kg, 60 mg/kg and 70 mg/kg, 70 mg/kg and 80 mg/kg, 80 mg/kg and 90 mg/kg, 90 mg/kg and 100 mg/kg, 100 mg/kg and 110 mg/kg, or 110 mg/kg and 120 mg/kg.
9. The use of any one of claims 1-8, wherein the antibody is to be administered once every 1, 2, 4, 5, 6, 7, or 8 weeks.

10. The use of any one of claims 1-8, wherein the antibody is to be administered twice every 1, 2, 4, 5, 6, 7, or 8 weeks.
11. The use of any one of claims 1-10, wherein the antibody is to be administered subcutaneously.
12. The use of any one of claims 1-10, wherein the antibody is to be administered intravenously.
13. The use of any one of claims 1-12, wherein the Tau protein associated disease is a tauopathy.
14. The use of claim 13, wherein the tauopathy is a neurodegenerative tauopathy.
15. The use of claim 13 or claim 14, wherein the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy.
16. The use of any one of claims 13 to 15, wherein the tauopathy is Alzheimer's Disease or progressive supranuclear palsy.
17. The use of claim 16, wherein the tauopathy is Alzheimer's Disease (AD).
18. The use of claim 17, wherein the AD is early, prodromal, prodromal to mild, mild, mild to moderate or moderate.
19. The use of any one of the preceding claims, wherein the treating comprises slowing memory loss or retaining or increasing memory capacity, memory function, or cognitive function in the individual.
20. The use of claim 19, wherein memory capacity, memory function, cognitive function, or memory loss is assessed using one or more of Clinical Dementia Rating–Sum of Boxes (CDR-SB), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog).

21. The use of claim 20, wherein ADAS-Cog is ADAS-Cog 13.
22. The use of claim 20 or claim 21, wherein a decrease in CDR-SB score, or an increase in RBANS score, or a decrease in ADAS-Cog score following administration of one or more doses of the antibody indicates one or more of increased memory capacity, memory function, or cognitive function in the individual.
23. The use of claim 20 or claim 21, wherein a stable CDR-SB score, RBANS score, or ADAS-Cog score, a slowing of the rate of increase of a CDR-SB score or ADAS-Cog score, or a slowing of the rate of decrease of a RBANS score following administration of one or more doses of the antibody indicates one or more of slowed memory loss or retained memory capacity, memory function, or cognitive function in the individual.
24. The use of any one of claims 20 to 23, wherein the CDR-SB score, RBANS score, or ADAS-Cog score is compared to the respective score at baseline.
25. The use of claim 24, wherein baseline is prior to administration of the antibody.
26. The use of any one of any one of claims 20 to 25, wherein the memory capacity, memory function, cognitive function, or memory loss is assessed at least 13 weeks, at least 24 weeks, at least 25 weeks, at least 37 weeks, at least 49 weeks, at least 61 weeks, at least 69 weeks, at least 73 weeks, at least 85 weeks, at least 97 weeks, at least 109 weeks, at least 121 weeks, at least 133 weeks, at least 145 weeks, at least 157 weeks, or at least 169 weeks after the beginning of treatment with the antibody.
27. Use of a monoclonal antibody that binds human tau at a dose between 225 mg and 16800 mg, in the manufacture of a medicament for retaining or increasing one or more of memory capacity, memory function, or cognitive function or slowing memory loss in an individual with a Tau protein associated disease, wherein the antibody comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 20; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 21; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 22; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 23; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 24; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 25.
28. The use of claim 27, wherein memory capacity, memory function, cognitive function, or memory loss is assessed using one or more of Clinical Dementia Rating–Sum of Boxes (CDR-SB), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS-Cog).

29. The use of claim 28, wherein ADAS-Cog is ADAS-Cog 13.
30. The use of claim 28 or claim 29, wherein a decrease in CDR-SB score, or an increase in RBANS score, or a decrease in ADS-Cog score following administration of one or more doses of the antibody indicates increased memory capacity, memory function, or cognitive function, in the individual.
31. The use of claim 28 or claim 29, wherein a stable CDR-SB score, RBANS score, or ADS-Cog score, a slowing of the rate of increase of a CDR-SB score or ADAS-Cog score, or a slowing of the rate of decrease of a RBANS score following administration of one or more doses of the antibody indicates one or more of slowed memory loss or retained memory capacity, memory function, or cognitive function in the individual.
32. The use of any one of claims 28 to 31, wherein the CDR-SB score, RBANS score, or ADS-Cog score is compared to the respective score at baseline.
33. The use of claim 32, wherein baseline is prior to administration of the antibody.
34. The use of any one of claims 27 to 33, wherein the memory capacity, memory function, cognitive function, or memory loss is assessed at least 13 weeks, at least 24 weeks, at least 25 weeks, at least 37 weeks, at least 49 weeks, at least 61 weeks, at least 69 weeks, at least 73 weeks, at least 85 weeks, at least 97 weeks, at least 109 weeks, at least 121 weeks, at least 133 weeks, at least 145 weeks, at least 157 weeks, or at least 169 weeks after the beginning of treatment with the antibody.
35. Use of a monoclonal antibody that binds human tau at a dose between 225 mg and 16800 mg, in the manufacture of a medicament for reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual with a Tau protein associated disease, wherein the antibody comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 20; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 21; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 22; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 23; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 24; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 25.

36. The use of claim 35, wherein the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein is measured by positron emission tomography (PET) or by analysis of cerebrospinal fluid.

37. The use of any one of claims 27-36, wherein the antibody is to be administered at a dose of 225 mg, 675 mg, 1200 mg, 1500 mg, 2100 mg, 4200 mg, 4500 mg, 8100 mg, 8400 mg, or 16800 mg.

38. The use of any one of claims 27-36, wherein the antibody is to be administered at a dose between 4000 mg and 16800 mg.

39. The use of any one of claims 27-36, wherein the antibody is to be administered at a dose between 4000 mg and 8500 mg.

40. The use of any one of claims 27-36, wherein the the antibody is to be administered at a dose between 225 mg and 600 mg, 600 mg and 1000 mg, 1000 mg and 2000 mg, 2000 mg and 3000 mg, 3000 mg and 4000 mg, 4000 mg and 4500 mg, 4000 mg and 5000 mg, 4500 mg and 5000 mg, 5000 mg and 5500 mg, 5500 mg and 6000 mg, 6000 mg and 6500 mg, 6500 mg and 7000 mg, 7000 mg and 7500 mg, 7500 mg and 8000 mg, or 8000 mg and 8500 mg.

41. The use of any one of claims 27-36, wherein the antibody is to be administered at a dose between 50 mg/kg and 240 mg/kg.

42. The use of any one of claims 27-36, wherein the antibody is to be administered at a dose between 60 mg/kg and 120 mg/kg.

43. The use of any one of claims 27-36, wherein the antibody is to be administered at a dose between 2.5 mg/kg and 5 mg/kg, 5 mg/kg and 10 mg/kg, 10 mg/kg and 15 mg/kg, 15 mg/kg and 20 mg/kg, 20 mg/kg and 30 mg/kg, 30 mg/kg and 40 mg/kg, 40 mg/kg and 50 mg/kg, 50 mg/kg and 60 mg/kg, 60 mg/kg and 70 mg/kg, 70 mg/kg and 80 mg/kg, 80 mg/kg and 90 mg/kg, 90 mg/kg and 100 mg/kg, 100 mg/kg and 110 mg/kg, or 110 mg/kg and 120 mg/kg.

44. The use of any one of claims 27-43, wherein the antibody is to be administered once every 1, 2, 4, 5, 6, 7, or 8 weeks.

45. The use of any one of claims 27-43, wherein the antibody is to be administered twice every 1, 2, 4, 5, 6, 7, or 8 weeks.

46. The use of any one of claims 27-45, wherein the antibody is to be administered subcutaneously.

47. The use of any one of claims 27-45, wherein the antibody is to be administered intravenously.
48. The use of any one of claims 27-45, wherein the Tau protein associated disease is a tauopathy.
49. The use of claim 48, wherein the tauopathy is a neurodegenerative tauopathy.
50. The use of claim 48 or claim 49, wherein the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy.
51. The use of any one of claims 48 to 50, wherein the tauopathy is Alzheimer's Disease or progressive supranuclear palsy.
52. The use of claim 51, wherein the tauopathy is Alzheimer's Disease (AD).
53. The use of claim 52, wherein the AD is early, prodromal, prodromal to mild, mild, mild to moderate or moderate.
54. The use of any one of the preceding claims, wherein the medicament is to be administered with at least one additional therapy.
55. The use of claim 54, wherein the additional therapy is selected from neurological drugs, corticosteroids, antibiotics, antiviral agents, anti-Tau antibodies, Tau inhibitors, anti-amyloid beta antibodies, beta-amyloid aggregation inhibitors, anti-BACE1 antibodies, and BACE1 inhibitors.
56. The use of any one of the preceding claims, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 18 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 19.

57. The use of any one of the preceding claims, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 26 or SEQ ID NO: 27 and a light chain comprising the amino acid sequence of SEQ ID NO: 28.

58. The use of any one of the preceding claims, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 26 or SEQ ID NO: 27 and a light chain consisting of the amino acid sequence of SEQ ID NO: 28.

59. The use of any one of claims 1-58, wherein the antibody is an IgG1 or an IgG4 antibody.

60. The use of claim 59, wherein the antibody is an IgG4 antibody.

61. The use of claim 60, wherein the antibody comprises M252Y, S254T, and T256E mutations.

62. The use of claim 60 or claim 61, wherein the antibody comprises an S228P mutation.

63. The use of any one of claims 1 to 62, wherein the antibody is an antibody fragment.

64. The use of any one of the preceding claims, wherein the antibody binds each of monomeric Tau, phosphorylated Tau, non-phosphorylated Tau, and oligomeric Tau with a K_D of less than 100 nM, less than 75 nM, or less than 50 nM.

65. The use of any one of the preceding claims, wherein the antibody binds cynomolgus monkey Tau (SEQ ID NO: 4).

66. An anti-Tau antibody comprising HVR-H1 comprising the amino acid sequence of SEQ ID NO: 20; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 21; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 22; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 23; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 24; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 25 provided at a dose between 225 mg and 16800 mg for use in 1) treating a Tau protein associated disease; 2) reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein; or 3) slowing memory loss or retaining or increasing memory capacity, memory function, or cognitive function in an individual.

67. Use of an anti-Tau antibody comprising HVR-H1 comprising the amino acid sequence of SEQ ID NO: 20; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 21; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 22; HVR-L1 comprising the amino

acid sequence of SEQ ID NO: 23; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 24; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 25 for the manufacture of a medicament for 1) treating a Tau protein associated disease; 2) reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein; or 3) slowing memory loss or retaining or increasing memory capacity, memory function, or cognitive function in an individual, wherein the antibody is provided at a dose between 225 mg and 16800 mg.